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Road traffic accidents and psychotropic medication use in the Netherlands: a case-control study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Some psychotropic medications (e.g. benzodiazepines, sedative antidepressants, etc.) can impair cognitive and psychomotor functions and, therefore, endanger traffic safety.
- There is a lack of knowledge concerning the role in traffic safety of first and new generations of psychotropic medications, new and chronic users, young and old drivers, and polypharmacy.

WHAT THIS STUDY ADDS

- There is an increased risk of having a traffic accident after being exposed to some psychotropic medicine classes and, in particular, to SSRIs.
- Health care professionals and patients should be properly informed about the potential effects of some psychoactive medications on driving abilities.
- The role of SSRIs in traffic safety has to be investigated further.

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AIM

To examine the association between the use of commonly prescribed psychotropic medications and road traffic accident risk.

METHODS

A record-linkage database was used to perform a case-control study in the Netherlands. The data came from three sources: pharmacy prescription data, police traffic accident data and driving licence data. Cases were defined as drivers, who had a traffic accident that required medical assistance between 2000 and 2007. Controls were defined as adults, who had a driving licence and had no traffic accident during the study period. Four controls were matched for each case. The following psychotropic medicine groups were examined: antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants stratified in the two groups, SSRIs and other antidepressants. Various variables, such as age, gender, medicine half-life and alcohol use, were considered for the analysis.

RESULTS

Three thousand nine hundred and sixty-three cases and 18 828 controls were included in the case-control analysis. A significant association was found between traffic accident risk and exposure to anxiolytics (OR = 1.54, 95% CI 1.11, 2.15), and SSRIs (OR = 2.03, 95% CI 1.31, 3.14). A statistically significant increased risk was also seen in chronic anxiolytic users, females and young users (18 to 29 years old), chronic SSRI users, females and middle-aged users (30 to 59 years old), and intermediate half-life hypnotic users.

CONCLUSIONS

The results of this study support previous findings and confirm that psychoactive medications can constitute a problem in traffic safety. Both health care providers and patients should be properly informed of the potential risks associated with the use of these medicines.

Introduction

Impaired driving involving alcohol, illegal and legal drugs causes, each year, a great number of traffic accidents all over the world [1–6]. Alcohol is a recognized leading contributor to road accidents and the association between alcohol and traffic accident risk has been extensively demonstrated [1–4], but, on the contrary, except for a few active substances (e.g. benzodiazepines, sedative antidepressants, opioids), the evidence of the role of medicine is still limited [4, 5].

Epidemiological studies have shown a positive association between psychotropic medication exposure and the risk of having a traffic accident [1–10]. A substantial number of studies have reported an increased traffic accident risk associated with the use of benzodiazepines [4, 5, 11–14]; however, there is still uncertainty on the traffic accident risk associated with the exposure to other psychoactive medications [3–5, 11]. Owing to methodological limitations and data availability, there is limited evidence of the association between road accidents and some commonly prescribed psychotropic medications (e.g. antipsychotics, antidepressants, anxiolytics, etc.), and, especially, the role of their dose regimen, first and new generations of medications, new and chronic users, and polypharmacy [3–5, 7, 8, 11, 15–17].

The current pharmacoepidemiological study examined the association between road traffic accidents and the exposure to different psychotropic medicine classes. In particular, it focused on the impact of factors contributing to driving impairment (i.e. recency of the prescription, medication half-life, gender and age) on the risk of experiencing a motor vehicle accident.

Methods

Data sources

We performed a case–control study, using three existing Dutch databases (i.e. PHARMO, DVS, RDW), and focusing on a 7 year period (2000–2007).

PHARMO is a pharmacy dispensing database which covers a population of more than 3 million Dutch residents [18]. In the Netherlands people commonly register with one pharmacy and obtain all their medications from that pharmacy so that an almost complete medication history is available. Registration is irrespective of health insurance and representative for the general population [19, 20]. Medicines are coded with the Anatomical Therapeutic Chemical (ATC) classification system [21], and, among others, the dispensing date, the prescribed dosage, the dispensed quantity and the estimated duration of use are available. PHARMO only contains de-identified information. A unique patient identification number (PID) is assigned to each subject who is included in this database; the PID refers to unique patient information (e.g. date of

birth, initials, gender, etc.) that is used to perform probabilistic linkages [18].

The Dienst Verkeer en Scheepvaart (DVS) is the Dutch Traffic and Navigation Authority [22]. Its database contains data on all the traffic accidents that occurred in the Netherlands and required the intervention of the police. In particular, this database stores data on drivers who were involved in the traffic accident (e.g. initials, age, gender, etc.) as well as traffic accident details such as the date of accident, day of the week, weather conditions, light conditions, severity of injuries incurred and breath test for alcohol excess.

The Rijks Dienst Wegverkeer (RDW) is the Dutch Road Transport Authority [23]. Its database contains all the available data on registered vehicles, their owners, vehicle registration numbers and driving licence numbers.

Database linkage

The database linkage was carried out by a Trusted Third party (TTP), within the PHARMO Institute, which granted full compliance with the current Dutch privacy regulations.

The database linkage was carried out in two phases. In the first phase of the linking process, the DVS database was linked to the RDW database by following a deterministic linkage methodology (1:1) based on the driving licence numbers belonging to those subjects who were involved in a traffic accident, and, consequently, stored in both databases. In the second phase of the linking process, the DVS + RDW database was linked to the PHARMO database. This phase was based on a probabilistic record linkage technology which is a purely statistical methodology [24]. This technology is widely used to perform database linkages and has been described in detail elsewhere [24, 25].

Approximately 3% of the car accidents that occurred in the Netherlands, in the study time frame, could be included in the database linkage process.

Inclusion and exclusion criteria

Cases were defined as adults (18 years or older), who had a traffic accident attended by the Dutch police between 1 January 2000 and 31 December 2007. Based on the police data, at the time of the accident, the subjects were driving, and, after their traffic accident, medical assistance was received and the seriousness of the accident was assessed. Cases were restricted to those subjects who were found negative for alcohol use.

Controls were defined as adults (18 years or older), who had a driving licence and had no traffic accident during the study period. Four controls were matched for each case; the matching was by gender, age within 5 years, zip code, and date of the accident of the correspondent case (i.e. the control's complete medication record had to be available in the PHARMO database at the time the correspondent case had an accident).

Study medications and exposure definitions

The following psychotropic medications, known to be of relevance for traffic safety, were included: antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics and sedatives (N05C), antidepressants stratified in selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants [i.e. non-selective monoamine re-uptake inhibitors; monoamine oxidase A inhibitors (MAOs); other antidepressants].

Anxiolytic and hypnotic benzodiazepines were stratified according to their half-life (short ≤ 12 h; intermediate >12 h and ≤ 24 h; long >24 h) [26].

Cases and controls were considered to be exposed if the medication was used during the week before the accident date (i.e. index date) (Figure 1). The day after the dispensing date was considered as the start of the therapy. If the therapy ended 2 days before the index date, the subjects were still considered as exposed (Figure 1). Medications dispensed on the day of the accident were excluded because it could not be established whether, for the cases, exposure occurred before or after the car crash.

New users were defined as subjects who used a driving impairing medication in the week before the index date, started their therapy up to 2 weeks before the index date, but did not receive any prescriptions for this medication in the 6 months before the initiation of the therapy. Chronic users were defined as subjects who used a driving impairing medication in the week before the index date and also used this medication in the 6 months before the index date (Figure 1).

Monotherapy was defined as the use of only one study medication and combination therapy was defined as the concomitant use of at least two study medicines.

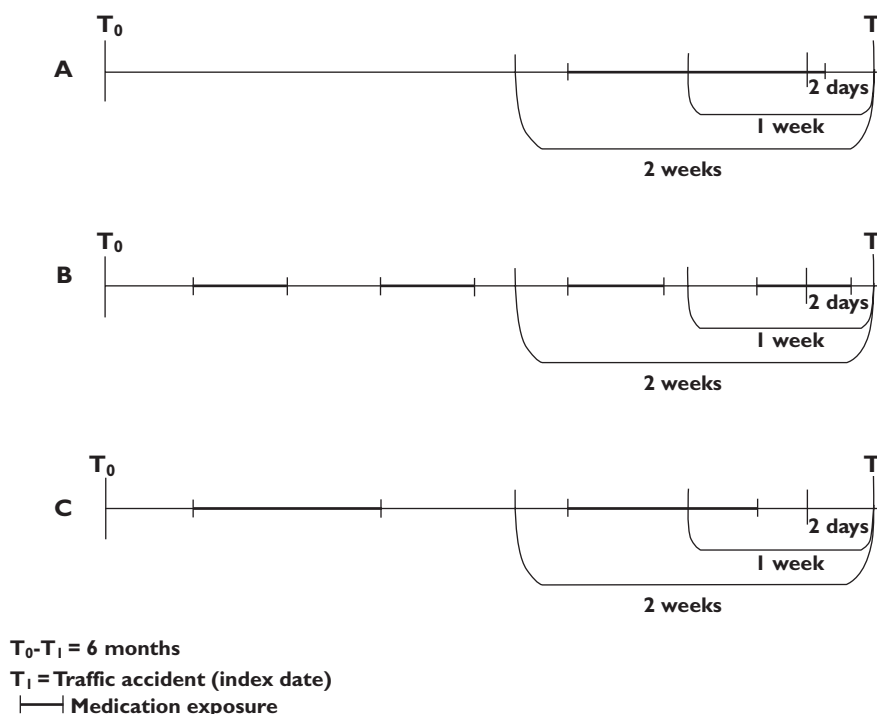
Statistical analysis

The statistical analysis was performed by using the statistical package SPSS (SPSS 16.0 for Windows).

Descriptive statistics were used to examine both accident and demographic characteristics of cases and controls.

Logistic regression analysis was used to calculate the odds ratios (ORs) of a traffic accident after exposure to the study medications. The case-control status was used as a dependent variable. The analysis compared the odds of exposure to the study medications among the cases with the odds of exposure among the controls. Exposure to one of the study ATC groups (e.g. SSRIs) was compared with the absence of exposure to the ATC groups of interest. Driver and medication characteristic stratifications were performed (i.e. medication user type; gender, age and benzodiazepine half-life) and adjusted ORs were computed (combination therapy adjustment). ORs were adjusted for psychotropic drug polypharmacy because it is well known that the concomitant use of medications can increase the risk of adverse effects, medicine interactions and, consequently, lead to an increased risk of traffic accidents [11, 14, 20].

95% confidence intervals (CIs) were calculated for all ORs to establish whether the findings were statistically significant.

**Figure 1**

Medication exposure (cases and controls). (A) New user – exposed, (B) chronic user – exposed and (C) chronic user – not exposed

The study research protocol was reviewed by the Medical Ethics Committee of the University Medical Centre Groningen (UMCG), the Netherlands, which resulted in the decision that, according the Dutch Medical Research Involving Human Subjects Act (WOM), this case–control study did not need an ethical approval.

Results

Data on 155 470 traffic accidents were available in the DVS database whereas 64 937 licence numbers were associated with a traffic accident in the RDW database during the years 2000–2007. After the first phase of the linking process, data on 90 533 traffic accidents were used in the second phase of the linking process. After this second phase, 3963 traffic accidents that satisfied the study inclusion criteria were available.

With respect to the control selection, in the first phase of the linking process, 6 916 598 driving licence holders who did not have a traffic accident in the years 2000–2007 were selected from the RDW database. After the second phase of the linking process, a database consisting of 858 039 subjects was available to perform the final control selection. This led to the selection of 18 828 controls corresponding to the inclusion criteria.

Therefore, our final study population consisted of 3963 cases and 18 828 controls.

Eight-hundred and twenty-one cases were excluded because they were either positive for alcohol (485 cases) or had no data on alcohol use (336 cases).

Cases were mainly males (males = 62.5%) and they mostly belonged to the age group 30–60 years (<30 years = 28.7%, 30–60 years = 53.9%, >60 years = 17.4%).

Table 1 presents the accident characteristics of the cases. From this table it can be seen that accidents were equally distributed during the four seasons, they mainly occurred on week days, with dry weather conditions, at daylight, and between 13.00 h and 19.00 h. According to the police report, the majority of the accidents were classified as either serious or moderately serious and, consequently, the subjects were transported to the hospital to receive further medical assistance.

Two-hundred and thirty-seven cases and 967 controls were exposed to monotherapy of one of the study medications, and 76 cases and 236 controls were exposed to combination therapy.

Table 2 shows in detail the medication exposure of cases and controls. It can be seen that anxiolytics were the most represented psychoactive medications, in both cases and controls, followed by SSRIs, and hypnotics and sedatives.

Table 2 also presents the crude and adjusted ORs for road traffic accidents related to psychoactive medication use, stratified by user-type, gender and age.

A significant increased traffic accident risk was seen for anxiolytics and SSRIs.

Table 1

Accident characteristics (cases only)

Accident characteristics (n = 3963)	n (%)
Season	
Winter	963 (24.3)
Spring	1019 (25.7)
Summer	881 (22.2)
Autumn	1100 (27.8)
Weather	
Dry	3199 (80.7)
Rain	635 (16.0)
Snow/Hail	49 (1.2)
Fog	52 (1.3)
Hard wind	3 (0.1)
Missing	25 (0.6)
Week/weekend	
Week day	3044 (73.8)
Time	
01.00 h–07.00 h	249 (6.3)
07.00 h–13.00 h	1245 (31.4)
13.00 h–19.00 h	1803 (45.5)
19.00 h–01.00 h	666 (16.8)
Light	
Daylight	2865 (72.3)
Dark	872 (22.0)
Dawn	226 (5.7)
Seriousness	
Fatal	24 (0.6)
Seriously injured (Hospitalization >24 h)	1365 (34.4)
Moderately injured (First aid point or hospitalization <24 h)	1486 (37.5)
Slightly injured (Treated on scene)	1088 (27.5)

The data also illustrate that new users were associated with a higher traffic accident risk compared with no use, except for the SSRIs. However, this association was not statistically significant.

In relation to the gender stratifications, it can be seen from Table 2 that there was a statistically significant association between the risk of having a traffic accident and female anxiolytic, and SSRI users. On the contrary, no statistically significant association was found between male users of the study medications and traffic accident risk.

Lastly, analyses of medication exposure by age groups indicated that only young anxiolytic and middle-aged SSRI users were positively associated with a higher traffic accident risk.

Table 3 illustrates the crude and adjusted ORs for road traffic accident in anxiolytic and hypnotic benzodiazepine users, stratified by half-life. As can be seen from this table, a statistically significant association was only found in the case of exposure to intermediate half-life hypnotics.

Table 2

Exposed subjects [cases ($n = 3963$) and controls ($n = 18\,828$)], crude and adjusted ORs* for road-traffic accident in different psychotropic medicine group users, stratified user type, gender, and age

Medicine group	Cases (exposed) (%)	Controls (exposed) (%)	Crude ORs (95% CI)	Adj. ORs (95% CI)
Antipsychotics				
All exposed individuals	20 (0.50)	96 (0.51)	1.01 (0.62, 1.63)	1.31 (0.71, 2.42)
New users	1 (0.03)	3 (0.02)	1.61 (0.17, 15.48)	1.61 (0.17, 15.48)
Chronic users	19 (0.48)	93 (0.49)	0.99 (0.60, 1.62)	1.29 (0.68, 2.44)
Males	12 (0.30)	63 (0.33)	0.92 (0.50, 1.71)	1.00 (0.41, 2.41)
Females	8 (0.20)	33 (0.18)	1.17 (0.54, 2.54)	1.78 (0.75, 4.24)
<30 years	3 (0.08)	19 (0.10)	0.76 (0.23, 2.58)	2.41 (0.60, 9.66)
30–60 years	15 (0.38)	63 (0.33)	1.15 (0.65, 2.02)	1.32 (0.63, 2.75)
>60 years	2 (0.05)	14 (0.07)	0.69 (0.16, 3.04)	0.54 (0.10, 4.24)
Anxiolytics				
All exposed individuals	94 (2.37)	310 (1.65)	1.46 (1.16, 1.85)	1.54 (1.11, 2.15)
New users	15 (0.38)	41 (0.22)	1.77 (0.98, 3.20)	1.81 (0.71, 4.63)
Chronic users	79 (1.99)	269 (1.43)	1.41 (1.01, 1.83)	1.51 (1.06, 2.16)
Males	49 (1.24)	162 (0.86)	1.46 (1.06, 2.01)	1.22 (0.74, 2.03)
Females	45 (1.14)	148 (0.79)	1.47 (1.05, 2.05)	1.89 (1.21, 2.95)
<30 years	8 (0.20)	19 (0.10)	2.03 (0.89, 4.65)	4.02 (1.23, 13.19)
30–60 years	58 (1.46)	185 (0.98)	1.51 (1.12, 2.04)	1.51 (1.00, 2.28)
>60 years	28 (0.71)	106 (0.56)	1.28 (0.84, 1.94)	1.27 (0.65, 2.46)
Hypnotics and sedatives				
All exposed individuals	76 (1.92)	273 (1.45)	1.34 (1.04, 1.74)	1.39 (0.94, 2.07)
New users	6 (0.15)	21 (0.11)	1.38 (0.56, 3.42)	2.76 (0.81, 9.43)
Chronic users	70 (1.77)	252 (1.34)	1.34 (1.03, 1.75)	1.30 (0.86, 1.98)
Males	33 (0.83)	142 (0.75)	1.12 (0.77, 1.64)	1.21 (0.64, 2.28)
Females	43 (1.09)	131 (0.70)	1.59 (1.12, 2.24)	1.53 (0.93, 2.54)
<30 years	2 (0.05)	11 (0.06)	0.88 (0.2, 3.96)	0.97 (0.11, 8.27)
30–60 years	33 (0.83)	123 (0.65)	1.30 (0.88, 1.91)	1.40 (0.83, 2.37)
>60 years	41 (1.03)	139 (0.74)	1.42 (1.00, 2.02)	1.43 (0.77, 2.65)
SSRIs				
All exposed individuals	92 (2.32)	252 (1.34)	1.76 (1.38, 2.24)	2.03 (1.31, 3.14)
New users	7 (0.18)	16 (0.08)	2.11 (0.87, 5.14)	1.81 (0.48, 6.83)
Chronic users	85 (2.14)	236 (1.25)	1.74 (1.35, 2.23)	2.06 (1.30, 3.26)
Males	40 (1.01)	122 (0.65)	1.58 (1.11, 2.27)	1.46 (0.72, 2.97)
Females	52 (1.31)	130 (0.69)	1.93 (1.40, 2.67)	2.55 (1.46, 4.45)
<30 years	16 (0.40)	30 (0.16)	2.58 (1.40, 4.73)	3.02 (0.99, 9.23)
30–60 years	57 (1.44)	183 (0.97)	1.50 (1.12, 2.03)	1.74 (1.01, 2.98)
>60 years	19 (0.48)	39 (0.21)	2.35 (1.36, 4.08)	2.63 (0.97, 7.13)
Other antidepressants				
All exposed individuals	40 (1.01)	146 (0.78)	1.32 (0.93, 1.88)	1.45 (0.81, 2.58)
New users	3 (0.08)	7 (0.04)	2.07 (0.54, 8.00)	2.41 (0.22, 26.63)
Chronic users	37 (0.93)	139 (0.74)	1.29 (0.89, 1.85)	1.41 (0.78, 2.56)
Males	16 (0.40)	66 (0.35)	1.17 (0.68, 2.02)	1.61 (0.72, 3.59)
Females	24 (0.61)	80 (0.42)	1.45 (0.92, 2.29)	1.30 (0.56, 3.00)
<30 years	2 (0.05)	13 (0.07)	0.74 (0.17, 3.29)	4.83 (0.32, 77.21)
30–60 years	28 (0.71)	95 (0.50)	1.42 (0.93, 2.17)	1.48 (0.75, 2.90)
>60 years	10 (0.25)	38 (0.20)	1.27 (0.63, 2.55)	1.11 (0.32, 3.91)

*ORs adjusted for combination therapy. Bold = Statistically significant.

Discussion

The outcomes of this study showed that the use of psychotropic medications could place drivers at a higher risk for a traffic accident. In particular, the current study indicated that there was a statistically significant association between the risk of having a motor vehicle accident and the exposure to anxiolytics and SSRIs. The results of our research also showed a significantly increased traffic accident risk in case of chronic SSRI users, intermediate half-life hypnotic users, female anxiolytic and SSRI users and young

to middle-aged drivers (this latter association was statistically significant only for users of anxiolytics and SSRIs).

Contrary to expectations, our study revealed a significant association between the risk of being involved in an accident as a driver and the exposure to SSRIs (OR = 2.03, 95% CI = 1.31, 3.14). Although these findings differ from previous studies which showed no increased risk of road-traffic accidents in SSRI users [4, 5, 7, 8, 11, 27], they are in line with those of Rapoport *et al.* and Hooper *et al.* who, however, focused on very specific populations (i.e. patients with dementia and military population, respectively) [28,

Table 3

Crude and adjusted ORs* for road-traffic accidents in anxiolytic and hypnotic benzodiazepine users, stratified by half-life

Medicine group	Cases (exposed) (%)	Controls (exposed) (%)	Crude ORs (95% CI)	Adj. ORs (95% CI)
Anxiolytic benzodiazepines				
Short half-life	0	0	–	–
Intermediate half-life	42 (1.06)	222 (1.18)	0.91 (0.66, 1.27)	1.13 (0.73, 1.75)
Long half-life	26 (0.66)	84 (0.45)	1.50 (0.96, 2.32)	1.57 (0.82, 3.01)
Hypnotic benzodiazepines				
Short half-life	20 (0.50)	128 (0.68)	0.75 (0.47, 1.21)	0.79 (0.39, 1.60)
Intermediate half-life	6 (0.15)	4 (0.02)	7.24 (2.04, 25.68)	6.44 (1.44, 28.78)
Long half-life	31 (0.78)	138 (0.73)	1.10 (0.73, 1.60)	1.42 (0.80, 2.53)

*ORs adjusted for combination therapy. Bold = Statistically significant.

29]. Our results are also consistent with those of Orriols *et al.* who, however, did not specifically focus on SSRIs but on psychoanaleptics as a total group [10]. A possible explanation for our SSRI findings might be that a proportion of reported car accidents could have been intentional, and, therefore, associated with the risk of suicide in relation to antidepressant use [30,31] or with not properly diagnosed or treated depression which is well-known to play a causal role in suicidal deaths [32–34]. These results may also be explained by the fact that depression itself can affect driving abilities and driving related skills by causing, for example, confusion, poor concentration, and cognitive impairment [28, 35–37]. These outcomes may also be due to comorbid psychiatric conditions and coexisting medical illnesses, which often occur in conjunction with depression and can influence the ability to drive, as well [38]. Another possible explanation is that the side effects of a single SSRI could have accounted for the increased ORs of SSRIs [8] or it is also possible that these results are due to lack of therapy adherence which has been often seen in depressed patients and might result in more severe adverse drug events and treatment failure [39, 40]. Lastly, the observed increase in traffic accident risk could also be related to the fact that, generally speaking, SSRIs are considered to be unlikely to produce driving performance impairment and, therefore, patients continue to drive during their course of treatment, exposing themselves to a greater risk of being involved in a traffic accident.

Surprisingly, our study did not find a strong association between road-traffic accidents and anxiolytics, and hypnotics and sedatives (anxiolytics: OR = 1.54, 95% CI 1.11, 2.15; hypnotics and sedatives: OR = 1.39, 95% CI 0.94, 2.07, not statistically significant), which are both well-known driving impairing medication groups [4, 5, 7, 8, 11–13]. It is difficult to explain these results, but they could be related to the fact that these medicines can be often taken at subtherapeutic doses for different indications (anxiolytics) [41] or at night (hypnotics) [12], and expose their users to a lower impairment and, therefore, a decreased likelihood of experiencing a car crash. Another possible explanation for our findings could be that anxiolytic and hypnotic and

sedative users, following the advice of their health care providers, tend not to drive, and, consequently, could be less exposed to a motor vehicle collision risk [42].

With regard to the user type, our research showed that the risk associated with psychotropic medication users was the highest among new users, even though this association was not found to be statistically significant in any of the selected medication groups. On the contrary, our results showed a significant increased risk in chronic SSRI users (OR = 2.06, 95% CI 1.30, 3.26). Very little was found in the literature on these latter findings. Nevertheless, the observed increased risk in chronic users of SSRIs could be explained by residual depressive symptoms [27, 43] or it could be attributed to a not fully achieved clinical remission by antidepressant treatment.

On the question of medicine half-life, the current study found a strong association between the exposure to intermediate half-life hypnotics and traffic accident risk (OR = 6.44, 95% CI 1.44, 28.78), and a positive, but not statistically significant, association in case of long half-life anxiolytic exposure (OR = 1.57, 95% CI 0.82, 3.01). These ORs confirm previous research [7, 8, 12, 44–47] and might be due to the fact that benzodiazepines with an intermediate/long half-life might have a longer duration of action or might accumulate and cause excessive sedation, and, consequently, have an extended negative effect on driving performance [8, 44, 45, 48].

The current study also indicated that female patients were more often significantly associated with the risk of having a traffic accident than male patients. These findings do not support previously published studies which showed an increased accident risk in male patients [29, 46, 47, 49]. It is difficult to explain these outcomes, but they could be related to biological differences between females and males which might expose women to a greater risk of developing adverse medicine reactions than men [44, 50, 51]. Lastly, it is interesting to note that, according to our descriptive statistics, males were more often involved in a car crash than females. This rather contradictory result may be attributed to the fact that, on average, men drive more miles than women [52, 53] or to the higher propensity of

male drivers to engage in aggressive and risky behaviour [54] or to the proneness of female drivers to adjust their driving behaviour when using a driving impairing medication [55].

In reference to the age stratifications, we found that, generally speaking, the use of psychotropic medicines by young and middle-aged patients could account for a higher risk of motor vehicle crashes. It is possible that these results can be related either to the higher number of miles driven by the younger population (given that this population represents the working population) [52, 56] or to the fact that young/middle-aged subjects tend to use these medications intermittently or to start driving earlier while still being exposed to driving impairing medications, and, therefore, without having developed tolerance to these medicines [12, 57]. These findings are in agreement with earlier findings [12, 13, 46, 47, 49, 55] and are also reflected in the descriptive statistics of our study.

To conclude, a number of limitations need to be considered. First, a pharmacy dispensing database was used for our study. The fact that the prescribed medications were dispensed does not imply that the patient actually took these medications or used them according to the prescription or to the information that was stored in the PHARMO database. Second, both cases and controls mainly used their medications either on a low or regular dosage. Therefore, it was not possible to examine the role of high medication dosage which is also known to be related to an increased risk of road-traffic accidents [12, 44, 58]. Third, there was no possibility to obtain information on medications prescribed during recent hospitalization or the concomitant use of over the counter medicines which could also have played a role in endangering traffic safety. Fourth, no information was available on what medical condition the psychotropic medications were prescribed for or on patients' comorbidities which both might have biased our outcomes [5, 13, 47]. Fifth, it was assumed that cases and controls regularly drove a car. This was a rough assumption, based on that fact that both cases and controls had a driving licence, but there was no other possibility to gain better insight into the driving patterns of our study population. Sixth, it was not possible to assess other influential factors, such as number of miles driven, risk taking behaviour (e.g. illicit drug use among cases and controls, alcohol use among controls, speeding, etc.), driving conditions, driving patterns associated with periods of use and non-use of a medication, driving experience and skills, which can also play a role in endangering traffic safety [29]. Finally, the database linkage process led to a considerable loss of cases. This sometimes resulted in small numbers which did not allow proper stratified analyses and thus fully reliable outcomes (e.g. user type and age stratifications).

Despite of these limitations, it is important to underline that, to our knowledge, this matched case-control study is one of the first studies to examine the risk of having a

traffic accident associated with exposure to a large and comprehensive set of different driving impairing medications and to investigate the role of other influential predictors such as user type, gender, age and medication half-life. Furthermore, it is noteworthy to point out that our study used the data from a large and representative population, it combined different and reliable data sources, and it also focused on a broad time frame.

In conclusion, the results of this study confirmed previous findings and those of a recent French study [10] on prescription medicines and road traffic crash risk and contributed additional evidence that psychotropic medications can constitute a considerable danger for traffic safety, especially for patients with no medicine use experience, female, and young psychoactive medication users. The evidence from this study suggests that, on the one hand, drivers should be aware of the risk of accident involvement associated with different treatment conditions and receive proper counselling from their health care providers, and, on the other hand, physicians and pharmacists should be able to minimize the risk of patients causing traffic accidents while driving under the influence of psychotropic medications by providing accurate advice, choosing safer alternatives, monitoring their patients' driving experience with the medication, and, if needed, advising them not to drive until they are fit to drive.

It is recommended that more research should be undertaken to investigate further the effect of SSRIs in traffic accidents in order to understand better the extent to which these antidepressants can cause or contribute to accidents. Moreover, more work needs to be done to determine the role of medication dose and dose changes, non-psychoactive medicines, and medical conditions.

Competing Interests

There are no competing interests to declare.

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